

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference Nos: 94-0305 and 94-0308

Hermann Allgaier, Ph.D.
Dr. Karl Thomae GmbH
Birkendorfer Straße 65
88397 Biberach an der Riss
GERMANY

20 AUG 1996

Dear Dr. Allgaier:

This letter hereby issues Department of Health and Human Services Biologics License No. 1199, to Dr. Karl Thomae, GmbH, Biberach an der Riss, Germany, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture and import into this country for sale, barter, or exchange, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture and ship the product Nofetumomab and associated components for the preparation of Technetium Tc 99m Nofetumomab Merpentan. Technetium Tc 99m Nofetumomab Merpentan is indicated for the detection of extensive stage disease in patients with biopsy-confirmed, previously untreated, small cell lung cancer.

Under this authorization, you are approved to manufacture Nofetumomab and the kit for the preparation of Technetium Tc 99m Nofetumomab Merpentan (hereafter known as the kit). Final containers of Nofetumomab will be manufactured, formulated, filled, and lyophilized at your facility in Biberach an der Riss, Germany. The nonbiological components of the kit will be provided by you and contract suppliers as specified in your license application. Isopropyl alcohol and phenthioate ligand will be supplied by you; the stannous gluconate complex, glacial acetic/hydrochloric acid, sodium bicarbonate buffer and reaction and elution vials will be supplied by _____ and the anion exchange column will be supplied by _____. The final component containers will be labeled and packaged into the kit at your facility in Biberach an der Riss, Germany. The kit will be distributed by DuPont Radiopharmaceutical Division, DuPont Merck Pharmaceutical Company, Billerica, Massachusetts under the trade name Verluma™. DuPont Radiopharmaceutical Division also acts on your behalf to receive adverse experience reports.

You are not currently required to submit samples of future lots of Nofetumomab or the kit to the Center for Biologics Evaluation and Research (CBER) for release under 21 CFR 610.2 by the Director, CBER. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for the dosage formulation of Nofetumomab shall be 24 months from the date of manufacture when stored at _____ The date of manufacture shall be defined as the date of final sterile filtration of the formulated bulk. The formulated Nofetumomab bulk may be stored for up to 18 months at _____ The dating period for the kit shall be 24 months or less, dependent upon the shortest expiration date of any component in the kit. when stored at _____ The dating periods of the non-biological vial components when stored at: shall be: _____ for isopropyl alcohol, _____ for phenthioate ligand. _____ for glacial acetic/hydrochloric acid, _____ for stannous gluconate complex. _____ for sodium bicarbonate buffer, _____ for anion exchange column, and _____ for the reaction and elution vials. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

We acknowledge your written commitment of April 15, 1996, including:

1. To submit within six months of licensure a labeling supplement that proposes modifications to the package insert based upon the results of the combined analysis of the fully audited data from the 77 patients in the readministration study and the data submitted in your product license application.
2. To perform and submit the results of an analysis (with supporting clinical data) to assess the safety and efficacy of the product in a subset of human-anti-mouse-antibody (HAMA) - negative patients who were readministered the product. and if necessary to develop a protocol to assess the safety and efficacy of the product in HAMA - negative patients.
3. To submit a plan for identification of patients who are or have been HAMA positive based upon HAMA test results at your central laboratory, and to propose a clinical protocol to evaluate the safety and efficacy of your product in this patient population.
4. To provide an educational program for physician and technologist instruction in Technetium Tc 99m Nofetumomab Merpentan image interpretation which will include an educational manual, consultant physician(s), and training sessions at national scientific meetings.

We also acknowledge your commitment of June 28, 1996 to perform and submit on an annual basis, trend analysis on release tests for lots of Nofetumomab, and lots of the kit including nonbiological components.

We also acknowledge your commitment of August 19, 1996 to have available at the time of market launch, mutually agreed upon training for the radiopharmacist in the use of the kit to prepare the product.

Any changes in the manufacturing, testing, packaging or labeling of Nofetumomab, the kit, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12. Any addition or deletion of contract suppliers involved in the production of the kit will require the submission of appropriate supporting data in order to ensure continued compliance with the approved standards for the manufacture of the kit.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). These requirements became effective on December 27, 1994. All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed biologics license to the Director, Division of Application Review and Policy (HFM-585), Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment Licensing
and Product Surveillance
Center for Biologics
Evaluation and Research

Enclosure

cc: Dr. David R. Brill
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT 06877